REMARKS

In response to the Office Action of October 3, 2000, Applicant requests re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

***Priority***

The Examiner has acknowledged receipt of papers(Application No. 2,263,063 filed in Canada) submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

The Examiner has correctly pointed out that an application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Accordingly, the instant application has now been amended to reference Canadian Application No. 2,263,063.

***Information Disclosure Statement***

The Examiner has pointed out that the listing of references in the specification is not a proper information disclosure statement in that 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Copies of information disclosure statements filed 5/25/00-Paper #2 and 7/5/00-Paper #6, in parent application 09/510,700 have been included herein. The references cited were reviewed by the instant Examiner during prosecution of the parent application which review was prior to issuance of the instant Office action, but were not deemed pertinent.

***Drawings***

Objections to the drawings are noted and formal drawings are herewith submitted.

***Oath/Declaration***

A new oath or declaration has been required because the originally filed oath does not identify the post office address of each inventor.

Applicant submits herewith a copy of the oath which was approved by the Examiner in the parent application, S.N. 09/510,700. Since this is a divisional application and contains no new matter, a copy of the original oath is believed to be sufficient.

***Specification***

In the instant application, the Brief Description of the Drawings has been deemed to be misleading. Specifically, on page

6, lines 4 and 5 of the disclosure, Figures 3-10 are alleged to be represented by one description which implies that each of the graphs are identical or have minimal differences so as to constitute their grouping. However, the figures are further described on pages 25 and 26 of the disclosure and taught to be substantially different-data from different patients exemplifying different events.

In accordance with the Examiner's suggestion, Applicant has now amended the specification to incorporate the clarified descriptions on page 25-26 for each of figures 3-10 respectively in the Brief Description of the Drawings.

Furthermore, the Examiner noted that the instant application appears to have several related applications/patents that were not incorporated into section (b) Cross-References to Related Applications. (i.e. USP#s: 5,744,358 - 5,747,274 - 5,604,105 - 5,710,008 -5,290,678 - Application #s: 08/026,453 - 08/481,743).

As was agreed in the prosecution history of the parent application, these patents/applications will not be placed within section (b).

Additionally, the Examiner has noted the use of several trademarks in this application, and referenced the fact that they should be capitalized wherever they appear and be accompanied by the generic terminology.

Applicant has endeavored to amend the specification

accordingly. If any omissions still exist, Applicant request that the Examiner contact Applicant's representative for prompt correction of the informalities.

***Rejections under 35 USC 112***

Claims 21-33 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner has indicated that:

I) Claim 23 is vague and indefinite in utilizing the phrase "blood products".

Because the term is not defined in the disclosure the metes and bounds can not be determined. The Examiner questions as to whether it is Applicant's intent to claim any material containing blood, any product useful in blood analyses, or any product derived from blood.

II) In claim 28, the use of "same sample" is deemed to be vague and indefinite because it is deemed to be unclear as to what is encompassed by the phrase. The Examiner questions as to whether the "same sample" wording is directed to separate aliquots from the same sample wherein the reaction for each marker is separately analyzed or does same sample refer to a single reaction wherein all the markers are added to a single sample. Furthermore, with regard to page 16, line 1, of the specification, the Examiner points out

that samples were centrifuged and aliquots of serum were frozen for further analyses. The Examiner suggests that if applicant intends to claim same sample aliquots it is suggested that the claim language recite this to eliminate any ambiguity.

III) Claim 24 is deemed to be vague and indefinite in the use of the acronym HT7. The Examiner questions as to whether the term is defined by any prior art teaching. The Examiner goes on to require that the term should be defined in its first instance.

IV) Claims 21 and 24 recite "combinations thereof'. The Examiner indicates that the claims are not clear as to what combinations are being claimed, further indicating that it appears that any combination of any of the recited proteins or any additional composition containing any of the recited proteins would meet the limitation of this claim. The Examiner concludes that no specific guidance was provided through a clear definition of what "combinations thereof"is meant to entail and requires further explanation.

V) Claims 26 and 27 are drawn to a method that requires a secondary marker with the "same specific cell type" as the other markers utilized in the method.

This claim is deemed to be vague and indefinite because it is not clear as to what "specific cell type" applicant is referring. The Examiner suggests that applicant include the specific cell type to obviate this rejection.

Accordingly, the claims have been amended in order to obviate the Examiner's objections/rejections. If there are any additional modifications deemed necessary, it is requested that the Examiner telephone Applicant's representative to facilitate agreement on claim language and avoid any further delays in prosecution.

***Rejection under 35 USC 103(a)***

Claims 21-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Jackowski (U.S. Patent # 5,604,105) or Jackowski (U.S. Patent # 5,710,008 in view of Strand et al. (Stroke, Dallas, 1984, 15(10, pages 138-44), Fassbender et al. (J. Neurol. Science, 1997, 148(1), pages 101 -105), Huguet (Lyon Pharm, 1993, 44(3), pages 187-92-Abstract Only), Sulter et al. (Neurosci. Letters, 1988, 253(1) pages 71-73), or Yatsu et al. (Stroke, 1995, Vol.26, No. 1, page 177).

Jackowski (5,604,105) is deemed to teach a method which detects a minimum of three markers that together present data distinguishing between ischemic and non-ischemic events. (Column 9, lines 64-67). A sample such as blood is contacted with antibodies specific for at least three markers to form a binding partner-marker binding pair. This complex is reacted with a second capture antibody to form a multiple antibody-marker composition. Each of the markers are then simultaneously assessed to ischemic events. (column 10, 17-62).

Jackowski (5,710,008) is further alleged to disclose methods and kits to detect at least three different markers of ischemic disorders. In one embodiment the first marker is an ischemic marker, and the other two markers are specific for myocardial infarction (column 20, lines 34-51). Several ischemic markers and their time of appearance in cardiac events is listed in Table 3.

Jackowski (5,604,105) and Jackowski(5,710,008) are further deemed to differ from the instant invention in not teaching the use of stroke specific markers as defined by claim 1, step a.

However, the Examiner nevertheless alleges that each of the recited markers (i-iv) are well known in the art and have been shown to correlate well with stroke events. This fact is deemed to be supported by the following references:

Regarding, myelin basic protein, Strand et al. (Stroke) teach that myelin basic protein measurement is a good marker for predicting cerebral damage after stroke or cerebral hemorrhage (see abstract).

In the case of the S100 protein, Fassbender et al. (Journal of Neurol. Science) is deemed to teach that serial quantification of S-1 00 in peripheral blood sample both acute and subacute phases of ischemic stroke is a significant measure of infarctions while control patient samples did not contain detectable S-100 (see abstract).

Neuron-Specific enloase (NSE) is allegedly disclosed by the

reference of Huguet (Lyon Pharm.) as a significant tumor marker and possible indicator of neuronal damage in stroke patients (see abstract). Sulter et al. (Neurosci. Letters) also is deemed to disclose the utility of neuron specific enolase concentrations as a measure for ischemic stroke.

Lastly, Yatsu et al. (Stroke) is deemed to have identified brain endothelial cells as an important protein in stroke measurements (see abstract).

Therefore, it is the Examiner's position that it would have been obvious at the time of applicants' invention to use known markers for stroke (namely, myelin basic protein, S100 protein, neuronal specific enolase, and brain endothelial cells as taught by Strand et al., Fassbender et al, Huguet et al., Sulter et al., or Yatsu et al. in either method of Jackowski (5,604,105) or Jackowski(5,710,008) because both methods of Jackowski teach that "many ischemic markers to which antibodies have been produced are well known in the art." (USP 5,604,105-Column 2, lines 28-30).

The Examiner then concludes that one having ordinary skill in the art would have been motivated to do this because Jackowski (5,604,105) and Jackowski(5,710,008) taught that their method was rapid, accurate, sensitive, and could distinguish an ischemic event. (USP5,604,105-Column 9, lines 44-62)

In setting forth this ground of rejection, the Examiner indicates that *"In the following rejections the claims are*

*interpreted to read on ischemic events. See claim 1, line 10."*

The Examiner, in applying the instant ground of rejection, interpreted the claims as referring to ischemic events and thus applied Jackowski (5,604,105) to teach a method which detects a minimum of three markers that together present data distinguishing between ischemic and non-ischemic events. (Column 9, lines 64-67) and Jackowski (5,710,008) to teach methods and kits to detect at least three different markers of ischemic disorders.

The Examiner correctly points out that Jackowski (5,604,105) and Jackowski(5,710,008) differ from the instant invention in *not teaching the use of stroke specific markers* as defined by claim 21, step a.

Neither Jackowski (5,604,105) nor Jackowski(5,710,008) teach or suggest a method as is now instantly claimed. Furthermore, one having ordinary skill in this art would have found no motivation in the primary Jackowski patents or related literature references, to suggest modifying the teachings of Jackowski '105 or '008 to include therein a method for

a. analyzing a body fluid of a patient to detect presence and concentration level of one or more ischemic marker proteins selected from the group consisting of myelin basic protein (MBP), the beta isoform of S100 protein (S100), neuronal specific enolase (NSE) and combinations thereof,

b. analyzing a body fluid of said patient to detect presence

and concentration level of a brain endothelial cell membrane protein, and

c. comparing the concentration level of any proteins detected in steps (a) and (b) to specific threshold values to verify the presence of statistically significant concentrations thereof of at least about two standard deviations above normal levels; and

d. assessing patient condition by comparing said presence or absence of statistically significant concentrations of said proteins in accordance with an analytical flow chart;

whereby differential diagnosis of an ischemic or hemorrhagic cerebral event is enabled.

Additionally, Jackowski fails to teach or suggest an assessment via the use of an analytical flow chart as instanatly claimed.

The substance of the algorithm taught by this flow chart, which was set forth in Figure 2 as originally disclosed by applicant, is further set forth in newly submitted claims 34-39.

It is respectfully submitted that the claims, as instantly amended, patentably distinguish over the references as applied. Thus, it is respectfully requested that these grounds of rejection be withdrawn and the application passed to issue.

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

IN THE CLAIMS:

Cancel claim 22.

Claim 21 (Amended). A method for the differential diagnosis of ischemic and hemorrhagic cerebral events comprising:

a. analyzing [the] a body fluid of a patient to detect [the] presence and concentration level of one or more ischemic marker proteins selected from the group consisting of myelin basic protein (MBP), the beta isoform[,] of S100 protein (S100), neuronal specific enolase (NSE) and combinations thereof,

b. analyzing [the] a body fluid of said patient to detect [the] presence and concentration level of a brain endothelial cell membrane protein, and

c. comparing the concentration level of any proteins detected in steps (a) and (b) to specific threshold values to verify the presence of statistically significant concentrations thereof of at least about two standard deviations above normal levels; and

[c. from the information obtained from said analyses, verifying the occurrence of an ischemic or hemorrhagic cerebral event and differentiating a particular type of cerebral event.]

d. assessing patient condition by comparing said presence or

absence of statistically significant concentrations of said proteins in accordance with an analytical flow chart;

whereby differential diagnosis of an ischemic or hemorrhagic cerebral event is enabled.

23 (Amended). A method as defined in claim 21 wherein said body fluid is selected from the group consisting of blood, blood [products] components and cerebrospinal fluid.

24 (Amended). A method as defined in claim 21 wherein said brain endothelial cell membrane protein is selected from one or more of the group consisting of Thrombomodulin, Glucose Transporter I in the dimeric or tetrameric form, Neurothelin[/HT7.], Gamma Glutamyl Transpeptidase, P-glycoprotein and combinations thereof.

26 (Amended). A method as defined in claim 21 further including:

analyzing said body fluid to detect presence and concentration level of a secondary marker protein [having the same specific cell type] which is cell type specific with respect to [as] one of said myelin basic protein, beta isoform of S100 protein or neuronal specific enolase whereby the time of onset of a hemorrhagic or ischemic cerebral event can be determined.

27.(Amended). A method as defined in claim 26 wherein said secondary marker protein has a higher molecular weight than said corresponding myelin basic protein, beta isoform of S100 protein or neuronal specific enolase [which has the same specific cell type].

28 (Amended). A method as defined in claim 21 wherein each of said analyses is carried out on a single sample of body fluid.

Claim 34 (New). The method in accordance with claim 21 wherein said step of assessing patient condition includes:

1) initially concluding that a brain injury has occurred when one or more proteins are present;

2) further concluding that said brain injury is a TIA if only NSE is present;

3) further concluding that said brain injury is a lacunar infarct if only a brain endothelial cell membrane protein is present;

4) further concluding that said brain injury is an intracerebral hemorrhage if MBP is present at a level equal to or greater than about 200 times normal levels;

5) further concluding that said brain injury is a cerebral infarct if S100 is present; and

6) further concluding that said brain injury is a subarachnoid hemorrhage if S100 and NSE are present.

Claim 35 (New). The method in accordance with claim 21 wherein said step of assessing patient condition includes:

determining when a brain endothelial cell membrane protein is present in addition to at least one ischemic marker protein and thereby concluding that an evolving cerebral infarct has occurred wherein the patient is a poor candidate for thrombolysis.

Claim 36 (New). The method in accordance with claim 21 wherein said step of assessing patient condition includes:

determining when S100 is present in addition to an increasing concentration of NSE absent the presence of a brain endothelial membrane cell protein and thereby concluding that an evolving cerebral infarct has occurred wherein the patient is a good candidate for thrombolysis.

Claim 37 (New). The method in accordance with claim 21 wherein said step of assessing patient condition includes:

determining when S100 is present alone or in addition to an increasing concentration of NSE or a brain endothelial membrane cell protein and thereby concluding that an evolving cerebral infarct has occurred wherein the patient is a poor candidate for thrombolysis.

Claim 38 (New). The method in accordance with claim 21

wherein said step of assessing patient condition includes:

determining when S100 is present in addition MBP at a level greater than two standard deviations and thereby concluding that severe cerebral edema is present.

Claim 39 (New). The method in accordance with claim 21 wherein said step of assessing patient condition includes:

determining when NSE is present along with at least one additional protein and thereby concluding that an evolving cerebral infarct has occurred; and

further determining if an elevated level of a brain endothelial cell membrane protein is present wherein the patient is a poor candidate for thrombolysis.

## SUMMARY

In light of the foregoing remarks and amendment to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Should any fee deficiencies have been inadvertently omitted, the Examiner is authorized to charge them to our Deposit Account #13-0439.

Respectfully submitted,

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